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<p>(21) International Application Number: PCT/EP97/04326</p> <p>(22) International Filing Date: 31 July 1997 (31.07.97)</p> <p>(30) Priority Data: 9616351.4 2 August 1996 (02.08.96) GB</p> <p>(71) Applicant (for all designated States except US): SMITHKLINE BEECHAM BIOLOGICALS S.A. [BE/BE]; Rue de l'Institut 89, B-1330 Rixensart (BE).</p> <p>(72) Inventor; and</p> <p>(75) Inventor/Applicant (for US only): COHEN, Joseph [US/BE]; SmithKline Beecham Biological S.A., Rue de l'Institut 89, B-1330 Rixensart (BE).</p> <p>(74) Agent: THOMPSON, Clive; SmithKline Beecham PLC, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p> <p>Y noCpG</p>
<p>(54) Title: VACCINE COMPOSITION AGAINST MALARIA</p> <p>(57) Abstract</p> <p>A vaccine composition useful in the prevention or treatment of malaria comprises a plurality of malaria-derived antigens in combination with an adjuvant which is a preferential stimulator of TH1 cell response.</p>		

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## VACCINE COMPOSITION AGAINST MALARIA

The present invention relates to a novel vaccine composition and to its use in medicine, particularly in the prevention of malaria infections.

5

Malaria, is one of the world's major health problems with 2 to 4 million people dying from the disease each year. One of the most acute forms of the disease is caused by the protozoan parasite, Plasmodium falciparum which is responsible for most of the mortality attributable to Malaria.

10

The life cycle of P. falciparum is complex, requiring two hosts, man and mosquito for completion. The infection of man is initiated by the inoculation of sporozoites in the saliva of an infected mosquito. The sporozoites migrate to the liver and there infect hepatocytes where they differentiate, via the exoerythrocytic intracellular stage, into the merozoite stage which infects red blood cells (RBC) to initiate cyclical replication in the asexual blood stage. The cycle is completed by the differentiation of a number of merozoites in the RBC into sexual stage gametocytes which are ingested by the mosquito, where they develop through a series of stages in the midgut to produce sporozoites which migrate to the salivary gland.

20

The sporozoite stage of P. falciparum has been identified as a potential target of a malaria vaccine. The major surface protein of the sporozoite is known as circumsporozoite protein (CS Protein). This protein from strain 7G8 has been cloned, expressed and sequenced (Dame *et al* Science 225 (1984) p593). The protein from strain 7G8 is characterised by having a central immunodominant repeat region comprising a tetrapeptide Asn-Ala-Asn-Pro repeated 37 times but interspersed with four minor repeats Asn-Val-Asp-Pro. In other strains the number of major and minor repeats vary as well as their relative position. This central portion is flanked by an N and C terminal portion composed of non-repetitive amino acid sequences designated as the repeatless portion of the CS protein.

30

It has been shown that irradiated sporozoites can provide significant protection against experimental human malaria (Am. J. Trop. Med. Hyg. 24: 297-402, 1975). However, production difficulties makes the use of irradiated sporozoite impractical from the point of view of producing a vaccine.

35

Several groups have proposed subunit vaccines based on the circumsporozoite protein. Several of these vaccines have undergone clinical testing; one is a synthetic

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peptide, the other is a recombinant protein (Ballou et al Lancet: i 1277 (1987) and Herrington et al Nature 328:257 (1987).

These vaccines were successful in stimulating an anti-sporozoite response.

- 5 Nonetheless, the magnitude of the response was disappointing, with some vaccinees not making a response at all. Furthermore, the absence of "boosting" of antibody levels on subsequent injections and results of in vitro lymphocyte proliferation assays suggested that T-cells of most of these volunteers did not recognise the immuno-dominant repeat. Nonetheless, one vaccinee in each study did not develop  
10 parasitemia.

International Patent Application No. WO 93/10152 (Smithkline Beecham Biologicals) describes and claims a hybrid protein comprising substantially all the C-terminal portion of the CS protein, four or more tandem repeats of the immunodominant  
15 region, and the surface antigen from Hepatitis B virus (HBsAg). Preferably the hybrid protein comprises a sequence which contains at least 160 amino acids which is substantially homologous to the C-terminal portion of the CS protein. The CS protein may be devoid of the last 12 amino-acids from the C terminal.

- 20 In particular there is described a protein which comprises a portion of the CS protein of *P. falciparum* substantially as corresponding to amino acids 210-398 of *P. falciparum* 7G8 fused in frame via a linear linker to the N-terminal of HBsAg. The linker may comprise a portion of preS2 from HBsAg.

- 25 A particular embodiment described in WO 93/10152 is the hybrid protein designated RTS. This hybrid consists of:

- A methionine-residue, encoded by nucleotides 1059 to 1061, derived from the *Saccharomyces cerevisiae* TDH3 gene sequence (nucleotides 1-1058 in this reading  
30 frame make up the TDH3 promoter itself). (Musti A.M. et al Gene 1983 25 133-143.
- Three amino acids, Met Ala Pro, derived from a nucleotide sequence (1062 to 1070) created by the cloning procedure used to construct the hybrid gene.
- 35 ◦ A stretch of 189 amino acids, encoded by nucleotides 1071 to 1637 representing amino acids 210 to 398 of the circumsporozoite protein (CSP) of *Plasmodium falciparum* strain 7G8 (Dame et al supra).

° An amino acid (Arg) encoded by nucleotides 1638 to 1640, created by the cloning procedure used to construct the hybrid gene.

5 ° Four amino acids, Pro Val Thr Asn, encoded by nucleotides 1641 to 1652, and representing the four carboxy terminal residues of the hepatitis B virus (adw serotype) preS2 protein (9).

10 ° A stretch of 226 amino acids, encoded by nucleotides 1653 to 2330, and specifying the S protein of hepatitis B virus (adw serotype).

WO 93/10152 further describes the expression of the hybrid protein in a recipient yeast strain which already carries in its genome several integrated copies of an hepatitis B S expression cassette. The resulting strain synthesises two polypeptides, S and RTS (or other hybrid protein of the invention), that spontaneously co-assemble  
15 into mixed (for example RTS, S) lipoprotein particles. These particles, advantageously present the CSP sequences of the hybrid at their surface.

It is an object of the present invention to confer immunity against *P. falciparum* and/or *P. vivax* infestations by immunization with a composition comprising a plurality of  
20 antigens in combination with an adjuvant which is a preferential stimulator of TH1 cell response.

Accordingly, the present invention provides a vaccine composition for use in the prevention or treatment of malaria, comprising a plurality of malaria-derived antigens  
25 in combination with an adjuvant which is a preferential stimulator of TH1 cell response.

Preferably, at least one of the antigens is a hybrid protein as defined above, such as RTS, more preferably in the form of mixed particles as defined above, such as RTS,S.

30 A further aspect of the invention provides a vaccine composition for use in the prevention or treatment of malaria, comprising a plurality of malaria-derived antigens, characterised in that at least one of the antigens is a hybrid protein as defined above, such as RTS, more preferably in the form of mixed particles as defined above, such as  
35 RTS,S.

The amount of antigen present in each vaccine dose is selected as an amount which induces an immunoprotective response without significant, adverse side effects in

typical vaccines. Such amount will vary depending upon which specific immunogens are employed. Generally, it is expected that each dose will comprise a total of 1-1000 $\mu$ g of protein, preferably 1-200  $\mu$ g most preferably 10-100 $\mu$ g. An optimal amount for a particular vaccine can be ascertained by standard studies involving  
5 observation of immune responses in subjects. Following an initial vaccination, subjects will preferably receive a boost in about 4 weeks, followed by repeated boosts every six months for as long as a risk of infection exists.

10 A further aspect of the invention lies in a method of treating a patient susceptible to plasmodium infections by administering an effective amount of a vaccine as hereinbefore described.

Adjuvants which are capable of preferential stimulation of the TH1 cell response are described in International Patent Application Nos. WO 94/00153 and WO 95/17209.  
15

A particular preferred adjuvant comprises QS21, an Hplc purified non-toxic fraction derived from the bark of Quillaja Saponaria Molina, and 3 De-O-acylated monophosphoryl lipid A (3 D-MPL), optionally together with an oil in water emulsion.  
20

3 De-O-acylated monophosphoryl lipid A is known from GB 2220211 (Ribi). Chemically it is a mixture of 3 De-O-acylated monophosphoryl lipid A with 4, 5 or 6 acylated chains and is manufactured by Ribi Immunochem Montana. A preferred form of 3 De-O-acylated monophosphoryl lipid A is disclosed in International Patent  
25 Application No. 92/116556.

QS21 is a Hplc purified non toxic fraction of a saponin from the bark of the South American tree Quillaja Saponaria Molina and its method of its production is disclosed (as QA21) in US patent No. 5,057,540.  
30

A preferred oil-in-water emulsion comprises a metabolisable oil, such as squalene, alpha tocopherol and tween 80. Additionally the oil in water emulsion may contain span 85 and/or lecithin.

35 The ratio of QS21 : 3D-MPL will typically be in the order of 1 : 10 to 10 : 1; preferably 1 : 5 to 5 : 1 and often substantially 1 : 1. The preferred range for optimal synergy is 2.5:1 to 1:1 3D MPL: QS21. Typically for human administration QS21 and 3D MPL will be present in a vaccine in the range 1  $\mu$ g - 200  $\mu$ g, such as 1-100 $\mu$ g,

preferably 10 µg - 50 µg per dose. Typically the oil in water will comprise from 2 to 10% squalene, from 2 to 10% alpha tocopherol and from 0.3 to 3% tween 80.

Preferably the ratio of squalene: alpha tocopherol is equal or less than 1 as this provides a more stable emulsion. Span 85 may also be present at a level of 1%. In

5 some cases it may be advantageous that the vaccines of the present invention will further contain a stabiliser.

Vaccine preparation is generally described in New Trends and Developments in Vaccines, edited by Voller et al., University Park Press, Baltimore, Maryland, U.S.A.  
10 1978. Encapsulation within liposomes is described, for example, by Fullerton, U.S. Patent 4,235,877. Conjugation of proteins to macromolecules is disclosed, for example, by Likhite, U.S. Patent 4,372,945 and by Armor et al., U.S. Patent 4,474,757.

15 Malaria-derived antigens useful in the present invention may be selected from the following:

1. A hybrid protein as defined above, such as RTS, more preferably in the form of mixed particles as defined above, such as RTS,S.

20

2. The TRAP of a cloned isolate of *P. falciparum* from Thailand known as T/9/96, and proteins having at least 80% homology thereto, and immunogenic derivatives including fragments thereof (described in International Patent Application Nos. WO 90/01496 and WO 91/11516 (3i Exploitation Limited), and WO 92/11868  
25 (US Navy)).

30

3. The 16kD protein described in International Patent Application No. WO 91/18922, and proteins having at least 80% homology thereto, and immunogenic derivatives including fragments thereof.

4. The apical membrane antigen-1 (AMA-1) of *P. falciparum* or *P. vivax*, and proteins having at least 80% homology thereto, and immunogenic derivatives including fragments thereof.

35

5. The circumsporozoite protein (csp) of *P. falciparum* or *P. vivax*, and proteins having at least 80% homology thereto, and immunogenic derivatives including fragments thereof.

6. The MSP-1 of *P. falciparum* or *P. vivax* (US Patent No 4,837,016), and proteins having at least 80% homology thereto, and immunogenic derivatives including fragments thereof.
- 5 7. Other exoerythrocytic stage proteins and immunogenic derivatives including fragments thereof.
- 10 8. Optionally, blood stage proteins and immunogenic derivatives including fragments thereof.

The term "immunogenic derivative" encompasses any molecule such as a truncated or other derivative of the protein which retains the ability to induce an immune response to the protein following internal administration to a human. Such other derivatives can be prepared by the addition, deletion, substitution, or rearrangement of amino acids or by chemical modifications thereof.

Immunogenic fragments of the protein, which may be useful in the preparation of subunit vaccines, may be prepared by expression of the appropriate gene fragments or by peptide synthesis, for example using the Merrifield synthesis (The Peptides, Vol 2., Academic Press, NY, page 3).

The immunogenic derivative can be a hybrid, that is, a fusion polypeptide containing additional sequences which can carry one or more epitopes for other Plasmodium immunogens, or other non-Plasmodium immunogens. Alternatively, the immunogenic derivative of the invention can be fused to a carrier polypeptide such as Hepatitis B surface or core antigen or to another carrier which has immunostimulating properties, as in the case of an adjuvant, or which otherwise enhances the immune response to the protein or derivative thereof, or which is useful in expressing, purifying or formulating the protein or derivative thereof.

The proteins or immunogenic derivatives thereof which are useful in the invention may be chemically conjugated to a macromolecule using a conventional linking agent such as glutaraldehyde (Geerlings et al, (1988) J, Immunol. Methods, 106, 239-244).



The following Example illustrates the invention:

### Example

5

#### Construction and expression of a recombinant TRAP.

This was prepared as described in WO 90/01496.

10 

#### Construction and expression of RTS,S.

This was prepared as described in WO 93/10152.

### Adjuvantation

15

Two adjuvant formulations were made each comprising the following oil in water emulsion component.

SB26: 5% squalene 5% tocopherol 0.4% tween 80; the particle size was 500 nm size

20 

SB62: 5% Squalene 5% tocopherol 2.0% tween 80; the particle size was 180 nm

#### Preparation of emulsion SB62 (2 fold concentrate)

25 

Tween 80 is dissolved in phosphate buffered saline (PBS) to give a 2% solution in the PBS. To provide 100 ml two fold concentrate emulsion 5g of DL alpha tocopherol and 5ml of squalene are vortexed to mix thoroughly. 90ml of PBS/Tween solution is added and mixed thoroughly. The resulting emulsion is then passed through a syringe and finally microfluidised by using an M110S microfluidics machine. The resulting oil droplets have a size of approximately 180 nm.

30

#### Preparation of emulsion SB26

This emulsion was prepared in an analogous manner utilising 0.4% tween 80.

35 

Other emulsions as depicted in the Table were made in an analogous manner.

To each 100ml of emulsion were added the two antigens (10mg of each antigen, equivalent to 50µg per dose) and mixed. This was combined with 100µg/ml of 3D-

MPL and 100µg/ml of QS21 to give the final formulation. Buffer was set according to salt content and pH.

TableVehicles two fold concentrated

5

Emulsions SB	Tocopherol %	Squalene %	Tween 80 %	Span 85 %	Lecithin %	Size
26	5	5	0.4	0	0	500 nm 90-100% 800 nm 10-0%
26.1	5	5	0.4	0	0.1	500 nm
63	5	5	0.6	0	0	500 nm
64	5	5	0.8	0	0	500 nm
61	5	5	1	0	0	250-300 nm
62	5	5	2	0	0	180 nm
40	5	5	0.4	1	0	500 nm 80-100% 800 nm 20-0%
40.1	5	5	0.4	1	0.1	500 nm
60	5	5	1	1	0	300 nm
65	5	5	0.4	1.5	0	500 nm
66	5	5	0.4	2	0	500 nm

**Reference Example** Various formulations of RTS,S

RTS,S is described in International patent application No. WO 93/10152 and was formulated for vaccination of balb/c mice. Five animals were in each group. 7 groups  
5 of animals received the following formulations

- |            |                                  |
|------------|----------------------------------|
| Group 1    | RTS,S SB62                       |
| Group 2    | RTS,S QS21 3D-MPL                |
| Group 3    | RTS,S QS21 3D-MPL SB62           |
| 10 Group 4 | RTS,S 3D-MPL A1(OH) <sub>3</sub> |
| Group 5    | RTS,S A1(OH) <sub>3</sub>        |
| Group 6    | Plain                            |
| Group 7    | Negative control                 |
- 15 (RTS,S - 5µg/dose, 3 D-MPL 5µg/dose QS21 5µg/dose)

The animals were inoculated and bled at 15 days post first immunisation and at day 7 and 15 post second immunisation and assayed for anti HBSAg antibody subtype. The emulsion SB62 when formulated with QS21 and 3D-MPL enhanced preferentially  
20 and in a synergistic fashion the IgG2a antibody response compared to SB 62 alone.

Enhanced IgG2a antibody response in mice is a measure of the ability of the adjuvant system to stimulate a TH1 type response.

## Claims

1. A vaccine composition for use in the prevention or treatment of malaria,  
5 comprising a plurality of malaria-derived antigens in combination with an adjuvant which is a preferential stimulator of TH1 cell response.
2. A vaccine composition according to claim 1, wherein the adjuvant comprises  
MPL.
- 10 3. A vaccine composition according to claim 1 or 2, wherein the adjuvant comprises QS21.
4. A vaccine composition according to any one of the preceding claims, wherein  
15 the adjuvant comprises an oil-in-water emulsion.
5. A vaccine composition according to any one of the preceding claims, wherein the malaria antigens are selected from the group consisting of:
  - 20 • a hybrid protein comprising substantially all the C-terminal portion of the CS protein, four or more tandem repeats of the immunodominant region, and the surface antigen from Hepatitis B virus (HBsAg);
  - the TRAP of a cloned isolate of *P. falciparum* from Thailand known as T/9/96, and proteins having at least 80% homology thereto, and immunogenic derivatives  
25 including fragments thereof;
  - the 16kD protein described in International Patent Application No. WO 91/18922, and proteins having at least 80% homology thereto, and immunogenic derivatives including fragments thereof;
  - the apical membrane antigen-1 (AMA-1) of *P. falciparum* or *P. vivax*, and proteins  
30 having at least 80% homology thereto, and immunogenic derivatives including fragments thereof;
  - the circumsporozoite protein (csp) of *P. falciparum* or *P. vivax*, and proteins having at least 80% homology thereto, and immunogenic derivatives including fragments thereof;
  - 35 • the MSP-1 of *P. falciparum* or *P. vivax* (US Patent No 4,837,016), and proteins having at least 80% homology thereto, and immunogenic derivatives including fragments thereof;

- other exoerythrocytic stage proteins and immunogenic derivatives including fragments thereof; and
- optionally, blood stage proteins and immunogenic derivatives including fragments thereof.

5

6. A vaccine composition according to any one of the preceding claims, for use in therapy.

10

7. Use of a vaccine composition according to any one of claims 1 to 5 in the manufacture of a medicament for use in the treatment or prophylaxis of malaria.

8. A method of treating or preventing malaria, which comprises administering to a patient in need thereof an effective amount of a vaccine composition according to any one of claims 1 to 5.

# INTERNATIONAL SEARCH REPORT

Intern. Application No.  
PCT/EP 97/04326

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K39/015 A61K39/002 A61K39/29 A61K39/39

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K C07K C12N G01N C12P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 17209 A (SMITHKLINE BEECHAM BIOLOG ;MOMIN PATRICIA MARIE (BE); GARCON NATHA) 29 June 1995 see claims 5,6,10 ---	1-8
X	WO 94 00153 A (SMITHKLINE BEECHAM BIOLOG ;PRIEELS JEAN PAUL (BE); GARCON JOHNSON) 6 January 1994 see claims 5,6,8,10 --- -/--	1-8

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

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- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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\*A\* document member of the same patent family

Date of the actual completion of the international search

9 January 1998

Date of mailing of the international search report

23.01.98

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# INTERNATIONAL SEARCH REPORT

Intern. Application No

PCT/EP 97/04326

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>HEPPNER D G ET AL: "Safety, immunogenicity, and efficacy of Plasmodium falciparum repeatless circumsporozoite protein vaccine encapsulated in liposomes."  JOURNAL OF INFECTIOUS DISEASES 174 (2).  AUGUST 1996. 361-366. ISSN: 0022-1899,  XP002048585  see page 361 - page 363  Materials and Methods</p>	1-8
Y	<p>SCHOEDEL F ET AL: "Immunity to malaria elicited by hybrid hepatitis B virus core particles carrying circumsporozoite protein epitopes."  JOURNAL OF EXPERIMENTAL MEDICINE 180 (3).  1994. 1037-1046. ISSN: 0022-1007,  XP002048586  see page 1039 - page 1042, right-hand column, last paragraph  Results and Discussion</p>	1-8
A	<p>WO 93 10152 A (SMITHKLINE BEECHAM BIOLOG)  27 May 1993  see the whole document</p>	
A	<p>US 4 837 016 A (HOLDER ANTHONY A ET AL) 6  June 1989  see the whole document</p>	
A	<p>WO 95 21192 A (SARAMANE PTY LTD ;ANDERS ROBIN FREDRIC (AU); CREWETHER PAULINE ELIZ)  10 August 1995  see the whole document</p>	5
A	<p>WO 86 05790 A (UNIV NEW YORK) 9 October 1986  see the whole document</p>	5
T	<p>WO 97 30159 A (PASTEUR INSTITUT ;UNIV NEW YORK (US); LONGACRE ANDRE SHIRLEY (FR);)  21 August 1997  see the whole document</p>	5
T	<p>WO 97 30158 A (PASTEUR INSTITUT ;UNIV NEW YORK (US); LONGACRE ANDRE SHIRLEY (FR);)  21 August 1997  see the whole document</p>	5



# INTERNATIONAL SEARCH REPORT

In international application No.  
PCT/EP 97/04326

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International Application No. PCT/EP 97/04326

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: 8

because they relate to subject matter not required to be searched by this Authority, namely:

Method of treatment of the human body

Remark : Although claim 8 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 97/04326

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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